REMARKS

Claims 1-20 are pending in the present application. .

At the outset, Applicants wish to thank Examiner Afremova for the helpful and courteous discussions with their undersigned Representative on January 6, 2006, February 8, 2006, and February 27, 2006. During these discussions, various amendments and arguments to address the outstanding rejections were discussed. The content of this discussion is believed to be reflected in the present response. Applicants also wish to thank Examiner Afremova for providing their undersigned Representative with an English translation of Jiang Duyin et al. Reconsideration of the outstanding rejections is requested in view of the amendments and remarks herein.

The rejections of: (a) Claims 4-8 under 35 U.S.C. §102(b) over Oliver et al; (b) Claims 4, 6, and 7 under 35 U.S.C. §102(b) over Takami et al; and (c) Claims 4-6 and 8 under 35 U.S.C. §102(b) over Jiang Duyin et al, are obviated in part by amendment and traversed in part.

The present invention relates to an acellular dermal matrix produced by a process comprising separating skin into an epidermis and an dermis; recovering the dermis; and decellularizing the dermis by simultaneously treating the dermis with a protease and a surfactant. The acellular dermal matrix of the present invention does not substantially contain cellular components, does not substantially contain basement membrane components, and retains a normal dermal matrix structure. (see Claim 4) Applicants submit that, for the reasons discussed below, none of Oliver et al, Takami et al, or Jiang Duyin et al disclose or suggest the invention as claimed.

Oliver et al discloses a process for production of an acellular dermal matrix (hereinafter referred to as "ADM") by treating mammalian fibrous tissue with only trypsin at below 20°C. At no point does Oliver et al disclose or suggest the simultaneous treatment of a protease (e.g., trypsin) and a surfactant. In fact, Oliver et al fails to disclose or suggest the inclusion of a surfactant. Furthermore, Oliver et al discloses that it is necessary to treat the dermis for a period of 48 hours or longer (column 2, line 60 - column 3, line 7 of Oliver et al).

The Examiner appears to recognize that this reference does not disclose or suggest the presence of the surfactant, but summarily disregards this deficiency in the disclosure of Oliver et al stating "product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. MPEP 2113." Applicants submit that the Examiner has misapplied this copied section of the MPEP to the facts of the present application.

With respect to product-by-process limitations, indeed the courts have enunciated that: "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claims is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985).

However, there are two important aspects to the foregoing. First, the products must be identical or an obvious variant thereof. Second, patentability of a product may not depend on its method of production, but the method of production cannot be disregarded if that method provides a *distinct structure or product*. Indeed, the Board and the Courts have said as much, which is set forth in MPEP §2113 in relevant part:

> "The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where... the manufacturing process steps would be ***expected to impart distinctive structural characteristics to the final product***. See, e.g. *In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979)... The Board stated that the dispositive issue is whether the claimed factor exhibits any unexpected properties compared with the factor disclosed by the prior art." (citing *Ex parte Gray*, 10 USPQ2d 1922 (Bd. Pat. App. & Inter. 1989) (***emphasis added***)

The foregoing is particularly relevant to the present application. Because the process disclosed in Oliver et al uses only trypsin, the treatment time inevitably becomes long. The skilled artisan commonly understands that the long treatment time denatures the ADM (see page 3, lines 12-14 of the present specification). In the present application, Applicants specifically demonstrate this effect and the problems in the ADM resulting by the method disclosed by Oliver et al.

Specifically, the method disclosed by Oliver et al is shown as method 4 (see page 18, lines 1-3 of the present specification). In method 4, it is shown that treatment with only trypsin for extended time periods as disclosed by Oliver et al results in denaturation of the ADM (i.e., 65.7% survival rate; see page 19, lines 16-32 of the present specification). In contrast, the ADM of the present invention presents the 86.8% survival rate. This high survival rate shows that the ADM retains a normal dermal matrix structure (see page 19, lines 9-15 of the present specification).

Therefore, the ADM disclosed in Oliver et al is denatured by the treatment with only trypsin. As such, the ADM disclosed in Oliver et al is structurally distinct from the ADM of the present invention, which retains the normal dermal matrix structure. Accordingly, the differences in the method steps cannot be disregarded when considering the patentability of the product-by-process limitations of Claims 4-8 (and Claims 15-20). Applicants submit that the rejection over Oliver et al is improper and should be withdrawn.

Takami et al suffers from a similar problem as that suffered by Oliver et al. Specifically, Takami et al discloses a method for a preparation of an ADM, in which a skin is first treated with dispase in phosphate buffered saline (PBS) at 4°C for 24 hours, followed by a second treatment with TritonX-100 in PBS for 1 hour at room temperature (see page 40, Method 1 of Takami et al).

Again, the Examiner is referred to the foregoing summary of the proper consideration of product-by-process limitations. Specifically, the Examiner is reminded that where the method steps would impart distinctive structural characteristics to the final product the method steps *cannot* be disregarded. This is, once again, dispositive in the case of Takami et al.

As stated above, Takami et al disclose a sequential treatment with a protease followed by a surfactant. This difference alone is sufficient to result in a distinct product. In the present application, Applicants specifically demonstrate the differences in an ADM resulting by the method disclosed by Takami et al (i.e., sequential treatment with dispase (protease) and Triton X-100 (surfactant)).

Specifically, the method disclosed by Takami et al is shown as method 1 (see page 17, lines 22-28 of the present specification). In method 1, the sequential treatment with dispase and Triton X-100 for 13 hours results in retention of basement membranes (i.e., 64.3% survival rate; see page 19, lines 16-32 of the present specification). In contrast, the ADM of the present invention presents the 86.8% survival rate. This high survival rate shows that the ADM retains a normal dermal matrix structure (see page 19, lines 9-15 of the present specification), whereas that of the method disclosed by Takami et al does not.

Further, with respect to the structural distinction between the present invention and Takami et al, in the method disclosed by Takami et al the treatment with dispase separates the epidermis and the dermis. However, the dermis is not recovered. The epidermis and the

dermis are treated with only TritonX-100 without removing the epidermis, thereby basement membranes remains over the dermis.

Within the ADM disclosed in Takami et al, type IV collagen was detected along the basement membranes of dermoepidermal junctions and along the basement membranes of former dermal vessels (see page 41, Result 2 of Takami, et al.). In contrast, within the ADM of the present invention, the expression of type IV is attenuated, and little of the basement membrane components remained (see page 18, lines 23-33 of the present specification).

In summary, the ADM disclosed in Takami et al contains the basement membranes because of the treatment with only TritonX-100 for both the epidermis and the dermis. Therefore, the ADM disclosed in Takami et al is different from the ADM of the present invention which does not contain the basement membrane components. Applicants submit that the rejection over Takami et al is improper and should be withdrawn.

The rejection over Jiang Duyin et al is similarly defective based on resulting differences in the products produced by the disparate methods of the present invention and this reference.

Jiang Duyin et al disclose a method for a preparation of an ADM. In Jiang Duyin et al, a skin is immersed in a digesting solution containing trypsin and TritonX-100 for 24h at 4°C, and an epidermis is removed and then all cellular components in the dermis are removed (see page 2, Materials and methods 1. of Jiang Duyin et al). Moreover, in Reference 1 (Jiang Du-yin et al, J. Fourth Mil. Med. Univ., 1990, 20(5) p. 371-374; copy **submitted herewith**) cited in Jiang Duyin et al, an epidermis is removed after a skin is digested with trypsin solution containing TritonX-100 at 4°C for 24 hours. Then, the dermis is treated with Dong Ling brand disinfectant for 4-6 hours (see page 372, Preparation of ADM of Reference 1).

Jiang Duyin et al and Reference 1 do not disclose a detailed method of how all cellular components in the dermis are removed or even if they, in fact, were. Dong Ling

brand disinfectant is not well known and/or readily available and the composition of this disinfectant is neither disclosed nor suggested in Jiang Duyin et al or Reference 1. As such, Jiang Duyin et al fails to provide an enabling disclosure to permit the skilled artisan to practice what is disclosed therein without undue experimentation or inventive contribution. Therefore, Applicants submit that Jiang Duyin et al should not even be cited as a reference for purposes of anticipation.

Moreover, within the ADM disclosed in Jiang Duyin et al, the presence of thin matrix membrane is verified on the surface of the dermis (see page 4, Results. 1). The thin matrix membrane, which presents on the surface of the dermis, is considered the basement membrane. In contrast, within the ADM of the present invention, the expression of type IV is attenuated, and little of the basement membrane components remained (see page 18, lines 23-33 of the present specification).

In summary, the ADM disclosed in Jiang Duyin et al contains the basement membranes because of the treatment with Dong Ling brand disinfectant. The ADM disclosed in Jiang Duyin et al is different from the ADM of the present invention which does not contain the basement membrane components. These structural differences are the result of differences in the methods and, therefore, Applicants submit that the rejection over Jiang Duyin et al is improper and should be withdrawn.

In view of the foregoing, Applicants request withdrawal of the anticipation rejections over Oliver et al, Takami et al, and Jiang Duyin et al.

The rejection of Claims 4-8 under 35 U.S.C. §103(a) over Takami et al and Jiang Duyin et al taken with Oliver et al and Livesey et al, is obviated in part by amendment and traversed in part.

Takami et al, Jiang Duyin et al, and Oliver et al are discussed above. None of these references disclose or suggest the product resulting from the process set forth in Claim 4.

Livesey et al is cited as providing evidence that dispase and trypsin are "alternative or equivalent proteases that are used for obtaining acellular dermal matrices... and... are applicable for dermal matrix preparation derived from animal skin including human." However, Applicants note that the method disclosed by Livesey et al is distinct from that of the present invention, as is the resultant product. In fact, the method disclosed by Livesey et al is directed toward isolation of collagen-based transplantable tissue. Indeed, Livesey et al disclose that it is the intent of their invention "is to ultimately remove this cellular component and to optimally preserve the extracellular matrix, therefore the stabilizing solution is formulated to minimize the initial cellular and subsequently the extracellular matrix damage. The extracellular protein and collagen matrix comprises a native three dimensional lattice that includes various proteins such as Type I collagen, Type II collagen, Type III collagen, Type IV collagen, elastin, laminin, teninsin and actinin, and proteoglycans." (see column 7, lines 41-51). At no point does this reference disclose or suggest how the skilled artisan would isolate an ADM according to the present invention.

Therefore, Applicants submit that even if the skilled artisan were to combine the disclosures of Oliver et al, Takami et al, Jiang Duyin et al, and Livesey et al, the presently claimed invention would not be obvious.

Accordingly, withdrawal of this ground of rejection is requested.

Finally, Applicants remind the Examiner that MPEP §821.04 states:

> ...if applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product claim ***will*** be rejoined. (*emphasis added*)

Upon a finding of allowability of the elected product claims, Applicants respectfully request rejoinder of the withdrawn process claims (Claims 1-3 and/or 9-13). Additionally, Applicants reserve the right to further amend the claims to assure compliance with MPEP §821.04 and/or introduce new method claims that meet the requirements of MPEP §821.04.

Applicants submit that the present application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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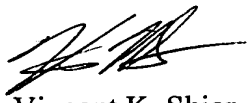

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